

Late Complications of Infection With *Opisthorchis viverrini*

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OPISTHORCHIS VIVERRINI is a parasite that commonly infects cats, dogs, and many fish-eating mammals; humans who ingest infested fish may become incidental hosts. As much as 90% of the population of northeastern Thailand and Laos harbors this parasite, and cholangiocarcinoma may develop in as many as half of those infected.¹⁻³ We report a case of cholangiocarcinoma associated with *O. viverrini* infection in a Laotian immigrant, and we discuss its public health implications.

Report of a Case

The patient, a 43-year-old woman who emigrated from Laos at age 35, was admitted to a hospital because of progressive fatigue and abdominal pain for two months and jaundice for two weeks. Her abdominal pain was sharp, unremitting, and bandlike across her abdomen. She reported having no bowel movements for five days before admission. She did not have diarrhea, melena, hematochezia, nausea, vomiting, fever, chills, or night sweats. She had a bout of mild upper abdominal pain as a young adult and was told she had "cysts in the liver." There was no known history of parasitic infection, blood transfusions, hepatitis, or tuberculosis. Her medications included ibuprofen as needed for pain and Chinese herbs. There was no family history of cancer or liver disease. Further relevant history included about a 9-kg (20-lb) weight loss attributed to a grief reaction following the death of her husband in a motor vehicle accident eight months before admission.

On physical examination, she was small, ill-appearing, and icteric, and she appeared older than her stated age. Her temperature was 37°C, pulse rate 98 beats per minute, blood pressure 115/65 mm of mercury, and respiratory rate 16 breaths per minute. Relevant findings included a protuberant abdomen, diminished bowel sounds, a positive fluid wave, and diffuse mild tenderness without guarding or rebound. Her liver was nodular and measured approximately 14 cm by percussion. The spleen was not felt. The results of a pelvic and rectal examination were normal.

Routine laboratory test results were remarkable for mild leukocytosis with a leftward shift, anemia, hy-

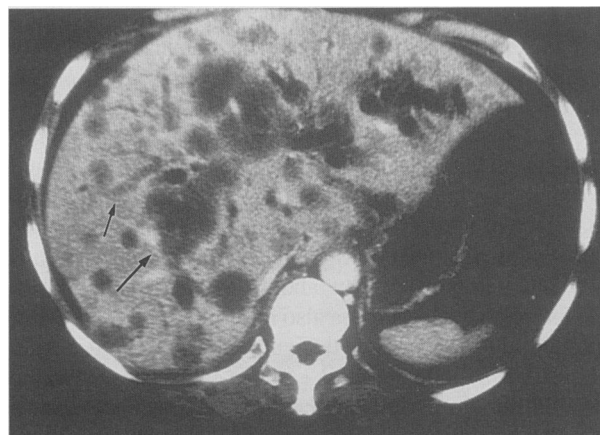


Figure 1.—An abdominal computed tomographic study shows multiple masses throughout the liver (long arrow) and dilated intrahepatic biliary ducts (short arrow).

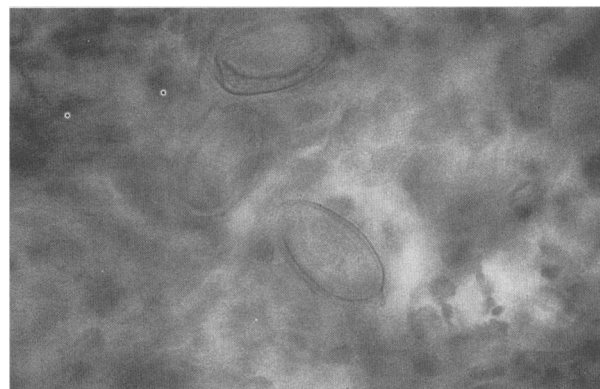


Figure 2.—Ovoid eggs typical of *Opisthorchis viverrini* are found in fine-needle aspirate of the patient's liver (original magnification, × 900).

pokalemia, and azotemia. The aminotransferase, alkaline phosphatase, lactate dehydrogenase, bilirubin, and tumor marker CA 125 levels were elevated (Table 1).

An abdominal ultrasonogram showed moderate ascites and a markedly heterogeneous texture of the liver that was suggestive of multiple hepatic masses. The gallbladder wall was circumferentially but mildly thickened to 4 mm, but no gallstones were seen. An abdominal paracentesis was done (Table 1), and cytologic examination of the fluid did not elicit malignancy. An abdominal computed tomographic (CT) scan showed multiple masses in the liver, dilated intrahepatic biliary ducts, and a thrombosed portal vein (Figure 1). A CT-guided fine-needle aspirate of a liver lesion showed a poorly differentiated adenocarcinoma, consistent with cholangiocarcinoma, and ovoid parasite eggs typical of *Opisthorchis viverrini* (Figure 2).

We informed the patient and her family of her poor prognosis and together decided on a conservative approach. She was treated for a urinary tract infection and given blood transfusions for anemia. A therapeutic large-volume paracentesis was done before she was discharged.

(Chiu A, Neff M, Garcia G: Late complications of infection with *Opisthorchis viverrini*. West J Med 1996; 164:174-176)

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TABLE 1.—Admission Laboratory Test Results in a 43-Year-Old Woman With Abdominal Pain and Jaundice

Laboratory Test, units*	Patient Value	Normal Value
Aspartate aminotransferase, U/liter.....	302	5-35
Alanine aminotransferase, U/liter.....	166	7-56
Alkaline phosphatase, U/liter.....	655	43-122
Lactate dehydrogenase, U/liter.....	4,802	297-537
Total bilirubin, $\mu\text{mol/liter}$ ((mg/dl).....	113 (6.6)	3-18 (0.2-1.0)
Albumin, grams/liter (grams/dl).....	31 (3.1)	33-50 (3.3-5.0)
CA 125 (U/ml).....	(702)	(0-16)
Ascitic fluid		
Leukocyte count, $\times 10^6/\text{liter}$ (/mm ³)..	1.7 (1,700)	
Differential cell count, fraction of 1 (%)		
Neutrophils.....	0.04 (4)	
Lymphocytes.....	0.53 (53)	
Monocytes.....	0.39 (39)	
Erythrocyte count, $\times 10^6/\text{liter}$ (/mm ³)..	1.5 (1,500)	
Lactate dehydrogenase, U/liter.....	1,650	
Total protein, grams/liter (grams/dl) ..	3.1 (31)	
Glucose, mmol/liter (mg/dl).....	5.6 (101)	
Albumin, grams/liter (grams/dl).....	14 (1.4)	

*Laboratory values are given in Système International (SI) units, with conventional units given in parentheses.

She was sent home with a patient-controlled anesthesia pump for administering subcutaneous morphine. As an outpatient, she received another blood transfusion and large-volume paracentesis was again done, but she died two weeks after hospital discharge. Permission for an autopsy was not given.

The public health department screened her family for stool ova and parasites. Three of her six children (ages 13, 18, and 24) and her brother had stool specimens said to be positive for *Clonorchis* species ova (30 by 15 mm), which are slightly larger but otherwise essentially indistinguishable from *O. viverrini* ova (30 by 12 mm).⁴

Discussion

Opisthorchis viverrini is an organism belonging to the class Trematoda (fluke). It is small (7 to 12 mm by 1.5 to 3 mm), yellow-red, leaflike in shape, rounded posteriorly, and tapered at its anterior end, with both an oral and a smaller ventral sucker. In endemic areas, people or other mammals become infected by eating raw or undercooked fish that carry the metacercariae. The ingested metacercariae excyst in the duodenum and migrate up the ampulla of Vater to the bile ducts, where they mature in about a month. The adult worms produce eggs that are then passed into the bile ducts and into the feces. The eggs hatch after being ingested by a *Bithynia* species snail, the first intermediate host. Cercariae emerge from the snail and are free-swimming organisms before invading freshwater fish and crayfish, the second intermediate hosts, where they encyst as metacercariae.^{3,4} The complete life cycle is about four months. Adult worms have a life span of more than ten years.

Opisthorchis viverrini is the most common food-borne parasite identified in Thailand, where an estimated 6 to 7 million people are infected with it. This costs the

country about \$65 million per year in wage loss and \$19.4 million per year in medical care.⁵ People from endemic regions (Thailand, Laos, Cambodia, and Malaysia) eat ground, raw, and salt-fermented freshwater fish daily.^{3,6} They usually become infected in their childhood or adolescent years and carry this infection throughout their lifetime if they are not treated. Each time an infected raw fish is ingested, the worm burden increases.³

Most persons infected with *O. viverrini* are asymptomatic. As the worm burden increases, usually in those older than 30 years, anorexia, weakness, nausea, diarrhea, flatulence, and episodes of right upper quadrant and epigastric pain may develop. On physical examination, acutely infected patients may have fever, jaundice, and tender hepatomegaly. Signs and symptoms due to complications of opisthorchiasis include cholecystitis, cholangitis, obstructive jaundice, cholelithiasis, and cholangiocarcinoma.^{1,3,4}

Although the results of laboratory tests of hepatic function are often within normal limits, acute infections may be associated with elevated serum bilirubin levels and other indices of abnormal liver function. Eosinophilia may be seen and, when present, is usually below 20%.^{3,4} Asymptomatic hepatobiliary abnormalities may be observed by ultrasonography: enlargement of the liver and gallbladder, decreased gallbladder contractility, the presence of sludge, and enhanced echogenicity of portal vein radicles.³ Pathologic changes in the bile ducts are related to the intensity and duration of infection. They include inflammatory cell exudation and desquamation of the epithelial lining, with the subsequent development of adenomatous hyperplasia and periductal fibrosis.^{3,4}

The diagnosis is usually made by identifying the eggs in stool specimens, although eggs will also be present in duodenal aspirates and bile from any source. Egg produc-

tion can be intermittent; thus, stool specimens from different days may have to be examined to make the diagnosis. If there is obstructive jaundice—as in our patient—eggs may not pass into the intestine, and stool specimens may be persistently normal.²⁴

In our patient, the diagnosis was established after a liver biopsy was done. We thought that her history, radiographic studies, and histologic findings collectively strengthened the diagnosis of adenocarcinoma from bile duct origin due to *O viverrini* infection. Furthermore, her CA 125 tumor marker level was high, and reports suggest that CA 125 may be a specific tumor marker for cholangiocarcinoma.^{7,8} We assume that the parasite eggs found in the stool specimens of the patient's family members are indeed a species of *Opisthorchis* and not that of *Clonorchis*. The two parasite eggs are difficult to distinguish, and the patient's family came from the same area in Laos where *Opisthorchis* species infestations are much more common than are infestations with *Clonorchis* species.

The carcinogenic event in cholangiocarcinoma associated with *O viverrini* is not known. Rapid cell turnover due to chronic cholangitis may enhance the unregulated growth of altered cells. An important interaction between the ingestion of nitrosamines (found in fermented fish) and *O viverrini* infection probably exists in the development of cholangiocarcinoma.^{3,9} The chewing of betel nut in the same population seems to be an independent risk factor for cholangiocarcinoma.⁶

The treatment of *O viverrini* infection is simple and consists of the administration of praziquantel, 25 mg per kg by mouth three times on a single day. Side effects from treatment are common and may include nausea, vomiting, abdominal pain, dizziness, myalgias, headache, and fatigue. They are generally well tolerated and usually abate within 48 hours.² The eggs generally disappear from the stools in a week, but symptoms and signs may take months to resolve. Alternative therapies include the administration of mebendazole, 30 mg per kg daily for 20

to 30 days, with cure rates of 89% to 94%; and albendazole, 400 mg twice a day for seven days, with cure rates of 63%.

It is evident that *O viverrini* infection can be fatal if untreated. Because people from Thailand and Laos have become common immigrants to our country, it is important for physicians in the United States to be cognizant of this possibly fatal disease. In 1994 the Santa Clara County (California) Refugee Program screened 2,101 Southeast Asian refugees for stool ova and parasites; 932 of these were positive. Many counties, however, do not screen refugees because of lack of funds. The positive stool specimens in our patient's family members underscore the importance of screening relatives from the same area and further justify the screening of immigrants as they enter the United States because this disease is easily treated before fatal cholangiocarcinoma develops.

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